DRUG INFORMATION ASSOCIATION

FDA/DIA SCIENTIFIC WORKSHOP ON FOLLOW-ON PROTEIN PHARMACEUTICALS

BREAKOUT SESSION C

PHARMACOLOGY-TOXICOLOGY STUDIES

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Marriott Crystal Gateway
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P R O C E E D I N G S

DR. EL-HAGE: Welcome. For the sake of time, we are going to get started. We are still waiting for one of our panelists to return, but the moderators for this group are myself, I'm the supervisory pharmacologist in metabolic and endocrine drugs; Andrea Weir, from CEDR, therapeutic proteins and ODE-6; Mercedes Serabian, from CEBR; Joy Cavagnaro, from AccessBio; and, Jim Green, from Biogen Idec.

We are going to run this session slightly different than some of the other breakouts, since we didn't have a plenary session this morning, and Jim Green is going to give some introductory overview slides of preclinical safety assessments for biologics, and then each of our other moderators will give a case example for discussion.

We have been missioned to approach this discussion based on low, moderate and high complexity proteins.

From our last discussion, it became clear that not everyone was in agreement that that should

be the approach that we take, but since our slides are made in that format, we are going to stick with that format.

A few ground rules before we start. We are seeking--our mission here was to get feedback from industry, both potential follow-on manufacturers and standard biotech manufacturers, on what might be a consensus opinion of what preclinical safety evaluations would be warranted for different types of molecules and different scenarios, in terms of what the biochemical characterization revealed.

We ask that speakers limit their comments to two to three minutes and that you identify yourself and your organization when you come to the microphone.

In addition, if you speak and you have a business card, we would ask that you provide a business card to our transcriber to aid in the generation of the minutes of the session.

Our first speaker will be Jim Green.

DR. GREEN: Thank you, Jeri. Welcome.

What I'm going to do in the next couple of minutes, because, as Jeri indicated, we didn't have a plenary lecture this morning, is just remind

everybody of a couple of the differences between small molecule biologic considerations, which are important when one thinks about the extent and scope of toxicologic assessment.

Some of these are listed on this slide. They include recognized limitations of animal models, the concept of relevant specie, the fact that some species essentially, on some of these molecules, are highly specie-restricted with respect to species that the desired pharmacology can be studied, and, also, the extent of certain animal models and how those animal models are used both in profiling potential efficacy, as well as potential safety issues, considerations that are somewhat unique to biologics.

Immunogenicity, we have already heard about that in the prior session and this morning and will tomorrow. Considerations related to immunogenicity are very important for biologics,

primarily with respect to understanding immunogenicity in the test system to the extent that pharmacological activity is compromised or not compromised or there is something related to an innate immune response that is invalidating conclusions that might be made regarding nonclinical assessment.

That is certainly not an issue that is front and center for small molecule safety assessment studies.

Also, one point which I think we may have some discussion on is that what kind of information can you get, qualitative or quantitative, or only qualitative, regarding immunogenicity profiles that might be elicited in animal studies; can they serve as a basis for comparing and contrasting one form of a molecule versus another, and that issue.

There are novel requirements for assays that are different from small molecules. These involve sensitivity, sometimes the availability. Certainly, when you are trying to profile a follow-on product relative to an innovator's

product, the issue you are confronted with immediately is one of assay similarity. Do you have to use one that is similar, identical, or not, or can you essentially employ state-of-the-art methodologies for that comparison?

Then, lastly, in some cases, there are what might be viewed as non-traditional dose response, the bell-shaped curve that is sometimes seen with biologics and how that essentially might complicate determinations regarding efficacy, therapeutic ratio, and the like.

Now, what types of studies are currently used to establish what is referred to here as bio similarity? These are indicated on this slide, and they range from, as we heard this morning, a whole host of biochemical characterization studies, but in essence, what their intent is to do is to confirm structural identity. Is it the same molecule or not?

Biological activity studies to confirm potency and maintenance of mechanism of action, and, hopefully, it would be a relevant mechanism of

action, one, two or three perhaps, but, again, these first two assessments are primarily laboratory-based, unless a biological potency assay, as an animal study, which, in some cases, they still are, pharmacokinetic and pharmacodynamic assessments to confirm dosing regimen, and the fact that the dosing regimen essentially of a follow-on product may be the same or may be different.

The concept of dose and disposition of a molecule is inherent and fundamental to considerations of issues related to therapeutic index, which are studied in the toxicologic evaluation, which the primary intent of those studies is to confirm therapeutic index and the safety profile, again, of the molecule, essentially, that is being developed relative to the molecule which has been established with an innovator's product.

Then, finally, the clinical assessment, which encompasses kinetics, safety and efficacy measures by a variety of approaches.

But in aggregate, these five buckets of

information, what are referred to as the technical assessment program and the focus of this panel's discussion today is on the toxicity, toxicologic evaluation.

Now, with respect to essential data requirements, one of the points where there is probably the most agreement, although I understand, in the session that we had next door, relative to the issue of one product, one process, there was anything but agreement, I guess you might say.

But nevertheless, that aside, it is, I think, generally accepted that a complete CMC characterization by state-of-the-art methodologies, as currently are done by the innovator today, tomorrow and to the end of the next decade, will be something that are required.

It is the additional data sets that are indicated on that technical assessment program which form the basis of an opinion of similarity. As I indicated, the panel focus today in this particular session is on preclinical safety assessment.

Now, when a toxicologic study is designed, there are several considerations which have to be thought about. First is, is there an animal model

that is viewed as relevant to the pharmacologic or toxicologic profile that has been established.

Can you assess that molecule or dosimetry in that molecule with readily available reagents? Are there specific concerns with the particular product that you are studying, both from a general toxicity perspective or a specific toxicity perspective that might be reflected in a unique product concern?

Then there is the issue of regimen or dose, dose multiple and route of administration. Just to put dose, essentially, in some perspective, as you heard this morning in the PK/PD session and, in particular, in Dr. Rogge's comments, the issue essentially of importance of kinetics in establishing dose and how you compare one dose as being equivalent to another is certainly front and center to considerations of concluding comparability or similarity, and that essentially

is related to comparisons of therapeutic ratio.

Now, continuing on specific design considerations, and you will hear the panel talk about that in some of the case studies, the issue of whether or not you're dealing with a product that has a large therapeutic index or a small therapeutic index is one. Does that affect, essentially, your considerations for the amount of toxicologic assessment that might be required?

We are focusing in these toxicology studies on the product itself and not so much the process impurities, but we do recognize, and I think it is a statement of fact that an impurity profile from a follow-on company, because you're starting essentially with--I mean, the process is different, new cell line, new reagents, new purifications, et cetera.

So the impurity profile will not be the same as that that is used in the innovator product, and how do you assess that.

I think it is the opinion of this panel that in cases where it can be done, that the

strongest comparison essentially is head-to-head comparison of the follow-on product to an innovator product, I mean, much like a clinical study where head-to-head comparisons essentially are the basis for conclusions.

That, essentially, scientifically, is the strongest comparison, and that would be one that would be encouraged. Then there is the issue of complexity of the protein. Should you be more or less concerned, essentially, about a product that is characterized as low complexity, moderate to high complexity, or very high complexity? Does that impact, essentially, your considerations for what might be viewed as minimum data requirements?

I think we'll talk about that with respect to the particular case studies.

So the question that has been charged to the panel is in which situation would animal studies be needed and why, and, as you see the case studies this afternoon, this is something which we will be addressing.

So Joy will take us through the complexity

issues and some other points.

DR. CAVAGNARO: Thank you, Jim. Again, when we consider which situation would animal studies be needed and why, we come up to the second question, why do we do animal studies anyway for the innovator, much less a follow-on.

So why do we do what we do? It's to communicate risk and that risk is communicated in two ways, and that's through the informed consent, so patients, now going on in the next session, talking about clinical pharmacology, they will sign an informed consent about a molecule that they will be receiving.

So insofar as we can provide them with as much information as we can in that molecule, then I think that that is important. The other area is in the product label.

So those two areas, we communicate risk. We present what we do, our animal studies.

You have heard the term case-by-case, and I think when we consider that, we consider the product, we consider the clinical indication, but,

more importantly, we consider the question.

So what is the concern? We are here because we want to somehow understand the uncertainty now that results from making a product, making a follow-on product, and how can we reduce the uncertainty of safety and effectiveness through the animal studies.

So we have been charged with looking at complexity. I think we found out in our previous session that it may be not so simple to just think about complexity, but I will go ahead and present you with the cases, these are in your notebooks, just briefly, and then we will get to the various case studies.

It is important to understand, when we say animal studies, that we don't, for especially in the area of the innovator protein-derived products, we take advantage of our animal studies and ask perhaps more questions within a single study.

So it isn't unusual for us to lump PK/PD, toxicology, local tolerance in one study. So I think that is an important take-home message when

we look at safety. And I think another take-home message is I don't think anybody wants to introduce an unsafe product into humans for the first time or to market.

So the examples that have been provided are the example of low complexity protein, with a fairly low molecular weight. It's nonglycosylated. It's limited heterogeneity, expressed in E. coli, lots of soluble hormone.

It has a well understood mechanism of action. There's a large body of pharmaceutical knowledge on the protein and pathway; the same excipients and formulation, and this is given by the IV route.

Protein complexity moderate to high. This would be a hypothetical receptor ligand, again, fairly low molecular weight. There are multiple innovators in this class. There's the glycosylated, then the cyolation impacts the PK, it's moderate heterogeneity, it's a CHO host, cytokine receptor interaction is well understood. It has a well defined organ toxicity, and there we

can think about therapeutic index.

It's nonredundant cell protein and the subQ route will be the route of administration, and the formulation is with a detergent.

Lastly, the protein of very high complexity. This is high molecular weight. There are multiple innovators, again, glycosylated, it's highly heterogenous. It binds one receptor through protein-protein interaction, and the second receptor for sulfated glycoforms, again, derived in CHO. The mechanism of action is only partly understood, and the IM route, and it is also formulated with detergent.

So these are kind of broad discussions in terms of complexity. Again, we heard this morning that even a monoclonal antibody which could be considered complex versus a small molecular weight E. coli derived protein could also require limited, in this case, preclinical testing.

In the case that was presented this morning, where it was a monoclonal antibody that bound to infectious agent, where there wasn't any

binding in a relevant animal species, it was non-target binding, tissue cross-reactivity.

One might look at tissue cross-reactivity and then assess from there the value of doing significant toxicology studies.

So, again, we will discuss now three case studies and then in the context of the case studies, we will consider protein complexity, as well as therapeutic index, and how we answer the questions in terms of what animal studies and how large a program to assure that we have reduced the uncertainties or, in other words, similarity of the follow-on and the innovator.

So Mercedes Serabian will go with the first study, first case.

MS. SERABIAN: I just want to say, just because it says case one, as Joy was saying, it doesn't necessarily mean it's associated with minimal complexity. I mean, I think that is an issue that definitely came up from the last session that we had, that complexity is not necessarily associated with the extent of characterization,

extent of preclinical studies that may be needed.

So this is--we are making some--I would almost call them assumptions, to a point, again, based on some of the conversation previously.

For biochemical characterization, basically, structural identification. We are assuming the innovator is equivalent to the follow-on product, and biological activity meaning potency, in vitro and/or in vivo, again, that is a point of discussion, is equivalent to the follow-on product.

We have sort of a starred line here, because I guess I can ask a couple of questions. One is if you've got these two points and these assumptions are made, biochemical, biological activity the same, if you will, do you have to go any further, do you have to generate PK studies, and then, in addition, additional preclinical studies, or go one step further and do nonclinical PK and if that is equivalent, which, in this case, it shows it to be, do you have to do additional nonclinical of preclinical toxicology studies.

And we have a toxicology evaluation. I like the term safety evaluation a little better, I think, just because I think that is more

encompassing than when people think tox.

So just open to discussion, basically, just people's viewpoints on that. Again, this is the time for you to speak up. We are here to listen.

So any comments or suggestions?

DR. REYNOLDS: Theresa Reynolds, Genentech. I think that I would argue that nonclinical PK comparisons are insufficient, that you really need to have a safety evaluation on top of that, because you need to really verify that the toxicity of the follow-on product is no more than the innovator's product, and that really speaks to TI and that speaks to ultimate clinical administration.

So you really can't get into the clinic before you understand some sense of the toxicity of your candidate relative to the innovator's product, and in order to do that, I would argue that you

need to do that head-to-head to have a good sense of what the innovator's product really does.

MS. SERABIAN: And, Dr. Reynolds, does the TI make a difference to you or it's not--

DR. REYNOLDS: Intuitively, I would have to say that the lower the TI, the higher the burden on verification that you had no--that you may have a better therapeutic index, you may have no greater toxicities.

On a lower TI, I still think that you need to verify that you do, in fact, see that; that you don't put patients at any additional risk.

MS. SERABIAN: And when you say lower the burden, in terms of just the extent of the animal studies?

DR. REYNOLDS: Maybe the extent of what you need to look for. Clearly, if you have a steep therapeutic index, you have places to look. So you really need to verify against those known end points.

MS. SERABIAN: Thank you.

DR. CHAMBERLAIN: Paul Chamberlain, MDS

Pharma Services. I think that is absolutely the right place to start the discussion.

I think the problem with molecular complexity is a spurious one, in structural terms, when it relates to toxicology, and I can think of a number of single-train FVs which are problematic, depending on the target specificity, on the one hand, and the problem of aggregation with these molecules.

So I think the answer to your question is, essentially, no. I think the focus is very much on the way Jim presented the scenario, which is a side-by-side comparative evaluation of therapeutic index as being a scientifically valid approach, and that will be linked to the mechanism of action of the molecule, its various functionalities, and that doesn't necessarily relate to the complexity, per se, of the structure.

DR. GREEN: Could I make one comment regarding these complexity issue? It didn't come up within the discussion earlier this afternoon, but did in a break, a discussion I was involved in.

I think maybe it just depends on what your background is and how you view--you're a biochemist and you're an analytical person. Essentially, you

see huge differences in your ability to characterize something like a low complex example that was described earlier and then one that might be moderately high.

I tend to look at that as different degrees of complexity, but all of them are still very complex, and I contrast that essentially to the small molecule.

Now, we heard from Dr. Kozlowski this morning, where he concluded that if we understood structure, that intuitively plays essentially to function, structure-function, and structure-function and structure-activity relationships we've been looking at in the small molecule world for a long time.

I think the experience to date suggests that maybe within a particular chemical class, now, these are small molecules, we can analyze them right down to the last atom, where these are,

within a particular chemical class, there is an ability, I think, to a fairly high degree of certainty, to understand essentially toxicity relationships when you move this metho group here or you move that group there.

You get outside of a chemical class and the diversity gets much broader, that ability to make those predictions falls apart. So it is very weak, even in that world.

All three of these examples, just from that perspective, are highly complex molecules and what we are asking, essentially, is on the basis of our ability to characterize those, can we, with a 100 percent certainty, conclude that just laboratory assessments alone are adequate.

Now, I just put that out for people to think about, because that dichotomy is one that is important to think about when you're thinking about what is necessary here.

DR. SOLTYS: Randy Soltys, from Genentech. I would agree, Jim, that whether you can characterize a molecule strictly on its biochemical

and biological profiles is questionable, and I think that really where the answers are going to be derived are in the clinic and that is where you find your safety and efficacy data to be coming from.

So we've got an ethical duty, I think, in terms of not jumping straight into humans and that we really need to do something before that.

I think there is an understanding that in animal studies, probably the way to go there, albeit that those animal studies may to be predictive for all the things we're interested in looking for, especially with regard to immunogenicity, but there is still a need to go down that route, I think, in terms of looking for off-target toxicity and having an understanding of the dosimetry compared to the innovator molecule.

So I just wanted to acknowledge that if we don't have a signal in those preclinical models, it doesn't necessarily give us any comfort, but rather than we need to forge on, do our clinical studies to see if there really are any substantive

differences.

If we do see a signal in the preclinical studies, it would just heighten our concerns and have an increased sensitivity regarding those findings.

MS. SERABIAN: From what I'm hearing, in terms of preclinical studies, you can't do the tox, the safety studies without the PK evaluation. Is that--I see some heads shaking. So that's either as a combined study, which would be nice to have, or if you have to do separate studies.

MS. SENSABAUGH: Hi. I'm Suzanne Sensabaugh, from Sicor, Inc., a subsidiary of TEVA Pharmaceuticals.

I'm probably the only non-pharm/tox person in this group, so I really apologize ahead of time is my question is naive or silly.

But my understanding is that we have an obligation to our human subjects or our normals that we use in our PK/PD studies to go into animals first before we dose in them. I think that is sort of the discussion that we are having right now.

We heard this morning, from one of our plenary session speakers, that if you can demonstrate authenticity of your active ingredient,

meaning that through analytical, physical, biological characterization, you know what you have and you know it behaves, that pharm/tox may be waived and that we can go to into humans and do a PK/PD study.

So I'm wondering if--I don't know if I'm permitted to ask the panel or maybe the audience to discuss perhaps that sort of scenario, because that isn't--I don't know if that would come in under this case.

It didn't seem that it would come in under case two or three. But that was put forth by a plenary speaker, someone who I assume has a lot more knowledge in the field than I do. So I would like to know under what cases or under what conditions would you not do an animal study and then go straight into humans.

MS. SERABIAN: Personally, I disagree with that speaker, but I don't know if anyone--

DR. EL-HAGE: I would just like to qualify that that speaker is a clinical PK person, not a pharm/tox person.

MS. SERABIAN: Again, scientific justification, I think, is also important, is also valid. So if you can potentially provide

justification, FDA, I think, would listen. But I don't agree with that.

DR. O'NEILL: Chuck O'Neill, BioMarin Pharmaceutical. I am in agreement with you, Mercedes, on that. I think animal studies should be done. I'm in agreement with the previous people who have commented that some minimalistic preclinical program needs to be done and depending on the initial findings, that would be expanded upon with subsequent studies prior to entry into man.

I think what we have to look at, though, is the immunogenicity question and comparison of immunogenicity across the two compounds. I know we're probably--this may or may not be a discussion point here, but one has to look for the assay

transferability from the innovator to the follow-on protein, because, frankly, anyone can make something look nonimmunogenic if you have a garbage assay, then to make sure that that has the same benchmark as far as how one looks at immunogenicity, not only in the nonclinical arena, but in the follow-on safety that would be taken in almost like a phase four type of mentality of the follow-on protein, to be looking at long-term safety of these molecules as they move forward.

That's the only comment I have. Thank you.

DR. STARK: Yafit Stark, from TEVA Pharmaceutical, and I'm working for both the innovative R&D, as well as for biologic generics.

I would like to ask a question to the podium. The question that I have to the podium is, first of all, how sensitive is the animal model to detect any changes regarding the biopharmaceutical generic versus the innovator?

The other question is what are the correlations between the animal findings versus the

clinical outcomes? How much are these animal models may be good predictor to clinical outcomes?

DR. CAVAGNARO: In terms of how sensitive the animal models, again, I think that that relies on the concept of understanding therapeutic index.

Certainly, if you have a wide therapeutic index, a toxicity study isn't a sensitive indicator of a change. So perhaps PK/PD would be more relevant. So I think that is the concept of the therapeutic index.

In terms of absolute predictive outcome, I think we're asking a couple of questions; one, is it different and whether or not the difference makes a difference, but I think in terms of this comparative session, we're not even--perhaps an animal model of disease is the most relevant to assess activity.

We haven't even gotten into it in terms of those are the most appropriate to look at toxicity, because on the one hand, we're looking at impurities or variants as a concern and not the active.

So I think that in terms of predictive value in animal studies, we are predicting--it is a challenge with animal studies, because, generally,

our tox studies are done in normal animals and people are sick that we treat.

So we're trying to predict not only cross-species, but cross-physiological states. So we're talking about standard tox studies. We haven't gotten into animal models of disease, and it could be that the animal model of disease is the most predictive of a finding in humans, but the question here is are two molecules different in terms of toxicity.

DR. SCHILDER: Paul Schilder, Genentech, Director of PK/PD Sciences.

I have the benefit of being both a clinical and a nonclinical pharmacologist. I've done both.

About the predictability of the animal studies, I would agree that we should do PK and PD in animals, as well as safety, but if it comes out negative or looks the same, it's not going to make

us feel any better in the clinic.

It will make us feel--it won't alleviate the need for clinical trials. I think people really need to make a line here.

We should do it to make sure we don't see differences, but if we don't see differences, please, don't assume we're not going to see those differences in the clinic.

DR. CAVAGNARO: Right. And I don't think we're saying that, but you have to tell me that if you're going to do the animal studies, they're going to be worth something. So, obviously, a negative is--but a positive would be cause for concern, because you could over-estimate, but we have to believe that if we're going to do them, they're worth something.

DR. SCHILDER: I agree that they should be done. If you see a positive or a toxilogical finding, I would worry. If I don't see one, I'm not going to substitute that for a clinical trial.

DR. GREEN: Can I respond, maybe comment not so much to that, but maybe to the earlier

questions? They were how sensitive are animal models to detecting these changes.

Generalizations, essentially, are dangerous, in any sense, because you can say animal model is not predictive and then somebody will say here is one that is a 100 percent predictive, it doesn't work in this model, it works.

Animal models, essentially, are predictive and then here is one that didn't. So I think there's always exceptions, and that's the problem with generalizations.

But my own personal experience, essentially, and I think someone commented on it earlier today, but certainly in the open session that was held back in September, we have had examples talked about and presented where laboratory studies that were reflected in the first two tiers there essentially failed to produce any evidence of nonequivalence.

So, essentially, the conclusion was comparability tests essentially were then performed in animals or in clinical settings and differences

were seen.

So you would conclude then that these in vivo tests were detecting something that the laboratory assessments failed to pick up, something of relevance, something of meaning.

So I think in that case, they had a higher degree of sensitivity.

The second point is how good is the prediction of--and I think human toxicity/pharmacology in animal models, and I think here, again, is a frame of reference for small molecules.

Probably the largest study that has been done outside of maybe a database that exists within companies or at the FDA is the ILSI/HESI study that attempted to determine how good essentially our toxicologic assessments done in nonclinical settings are at predicting human toxicities.

Depending on how the data was looked at, somewhere between, I think the number was 80 percent in the publication, so there's 20 percent of human toxicities essentially that weren't

predicted and when you start looking at those toxicity categories, then they're certainly symptomatic, headaches, those kind of things. Well, animals can't tell you that.

But there's always issues, essentially, that you're going to miss those. Now, with biologics, because, theoretically, we do know a little bit more perhaps about the biology, the pharmacology, receptor interaction, mechanism of action.

My own personal experience, if a similar kind of study, like the ILSI/HESI study, were done, I would bet that it's in excess of 80 percent that we would be predicting relevant human pharmacology to human toxicities.

In my own personal experience, we have highly predictive models. If it's a T cell depleter in humans, it's a T cell depleter in animals. You don't see--if you see attenuation of that response in animals, you will see attenuation of that response in the clinic.

So in that sense, they are very sensitive

for picking up relevant activities of the biologics.

DR. CAVAGNARO: Right. It might not be to the extent, it might be different, but the mechanism of action is still the same. Right.

DR. GREEN: The difference between molecule A and molecule B.

DR. ROGGE: I would just like to follow-up with something that the gentleman from Genentech brought up in the supplement presentation this morning. I like to use examples. I'm Mark Rogge, and I'm from ZymoGenetics.

I don't think I am speaking out of line here. This information is all public.

We are currently developing thrombin, recombinant human thrombin, and the product has not shown any immunogenicity at all in monkeys, the species we're using. It hasn't shown any immunogenicity at all in the human trials thus far.

We are going through process changes, as you would expect. We are going to, I'm sure, do many more process changes as the product gets onto

the market. Keep our fingers crossed.

We are going to continue to use animals before we ever go into a human with any new process.

The potential of immunogenicity could have very severe consequences. So irrespective of sort of the thoughts that have gone around, I think there are some very legitimate reasons to always probe, in an animal species, if there is a good reason, before you ever go into a human.

DR. KIM: My name is John Kim, from LG Life Sciences. I have actually three points to comment.

I agree that some form of the tox study will be required. My question to the panel and the audience, how much information do we need? Do we need the first set of tox information or some limited information, depending on the case you will be mentioning?

The second point is there is some discussion about we need to have some kind of head-to-head comparison against two compounds.

In the case of the immunogenicity study, that makes sense, whereas some other regular conventional tox study, whereas the innovator has

not done the head-to-head comparison, because there is nothing there, or they are developing an independent drug, so there was no requirement.

So do you want to have the head-to-head for the other type of tox study, as well?

And the last question, the last comment is in case of the immunogenic one, because of the different animal species we are using, some of it can be inherently immunogenic.

So when you give it to the human or it originated by the rat or others, then you form much more the immunogenic response, then how are we going to address those.

Maybe you can just comment on this.

MS. SERABIAN: I guess my initial general question is one back to the audience, because this is one thing we are asking, too, in terms of if animal studies are needed, which it seems I'm hearing general agreement.

To what extent are those studies--do you have to do? I think it depends on the product, for one thing. I think it depends on the therapeutic index. If it's low, then you're going to need to probably do more extensive series of studies and/or end points than you would if it's high.

I think it's a--I won't say case-by-case, but I think it depends on the product that you are evaluating.

DR. CAVAGNARO: Right. So let's just do hypotheticals, but with real products. So this isn't a regulatory stance, because it is so difficult not to speak in terms of specifics.

So let's take growth hormone. Growth hormone, there is a very good in vivo PD assay, rat weight gain, tibia, whatever, whoever does growth hormone. So one could envision that study looking at local tolerance, maybe doing some PK or whatever, that may be appropriate for growth hormone, let's say,

For GCSF, there's a good PD maker. GCSF is active in rodents. You can look at PD, you can

look at PK. Most of the toxicity is related to hematapoiesis, it's right there on the rat, you can tell it. GMCSF is specie-specific. It doesn't work in the rat. It works in monkeys.

In that study, you may have to do a monkey study and look at that end point. If antisense were a biologic, we know that the trigger is compliment activation in non-human primates. Rats are no good. You may have to do a tox model to look at a trigger of compliment activation, PK/PD, et cetera.

So whatever the concern is. So if it's a repro concern, if it's a general toxicity concern that you had with your active, then that would be something as a comparator.

Obviously, if your compound has been nontoxic in a tox study, I still question the value added of a tox study or the level of sensitivity, and all what you talked about was active and we have talked about that.

But then the other issue is, well, what about the process impurities, and then you can go

down another road in terms of what types of studies would we do process impurities, and we don't do tox studies for process impurities, generally, for innovators. We just don't do it.

Now, you could say you can address it within your tox model and we kind of look at that, but most of what you referred to as predictive value was predictive value of active, the exaggerated pharmacology, not predictive value of an impurity.

MS. SERABIAN: I mean, I think there are smart studies, not just check the box and do a standard tox study, but think about what your product is and what the innovator product has shown in terms of potential toxicities, potential risks, and then go from there as to how to design the study.

I mean, I don't think we'll get into details here as to study design. I think that is very specific. But I think it's an important point.

Do you want to take the immunogenicity

question that was brought up as to species? Do you want to do it, Jim?

DR. GREEN: The immunogenicity issue?

MS. SERABIAN: Yes.

DR. GREEN: Maybe if I can just briefly address where I think the discussion has gone.

Again, there are some, essentially, which will be on one camp say immunogenicity assessment in animals is totally irrelevant, you can only assess that in the clinic. I think ultimately--

MS. SERABIAN: I think the question, too, is in a particular species, like interferon in a monkey.

DR. GREEN: I'm sorry?

MS. SERABIAN: Like interferon in a monkey, for example, if these studies restrict, due to the development of antibodies to the product, then what do you--

DR. GREEN: Oh, in a qualitative sense. I was going to get there. Let me just jump to that.

I think what we're talking about, again, in a study paradigm where there is an opportunity

to perform a head-to-head assessment, that qualitative comparisons, essentially, on immunogenicity end points should be looked for and the first reason they should be looked for is because you can't make an interpretation about the validity of your test system unless you know something about the immunogenic response in that test system.

So, first, essentially, and that is clearly stated in the ICHS-6 document, which applies essentially to these follow-on assessments.

Now, if you view immunogenicity as a signal, just like any other toxicity signal, which I think that's how it should be looked at, and the other toxicity signals that you're concerned of are related to what you know about the product, you may essentially be able to see a different expression of that signal. It may be intensity, it may be something else.

However, I would posit the example of--the one I like to think about essentially are some of the humanized antibody constructs, where the data

that essentially is available in animals, as well as in humans, show, surprisingly, to many people, a very, very non-immunogenic profile.

So if you were a follow-on company making a particular antibody construct and you had essentially incidence rates that you're talking about, let's say less than one percent, and you tested essentially your product versus the innovator's and you duplicated the one percent, less the one percent incidence rate, in that non-clinical model and your product showed essentially a 15, 20, some other number, some other strikingly high number, relative, that should be a cause for concern. That should be a signal.

So within the context essentially of the kind of hierarchical assessment, it is looked at and I think you would conclude that the extent of clinical assessment that would be warranted in that case would be more and earlier.

In the absence of that, does that totally get you out of essentially assessing that end point? I think not, but how you do it may be a

subject of discussion.

MS. SERABIAN: Any other comments? If not, we'll move on to the next.

DR. WEIR: Moving on to case number two. In this case, with the biochemical characterization, it was shown that the innovator was not the same as the follow-on product; that is, the follow-on product was different.

I think this morning there was a very nice presentation of the way that these products are characterized biochemically.

In this case, there were differences detected. However, in the case of the biological activity, the innovator and the follow-on product were shown to be similar.

With regard to the nonclinical PK comparison, again, the two products were shown to be similar.

So in this case, with this being the scenario for the follow-on product, again, the questions are should there be a toxicology evaluation done, and would the extent of the

toxicology evaluation vary with regard to therapeutic index and complexity of the molecule.

Any takers?

DR. O'NEILL: Chuck O'Neill, BioMarin. This represents, to me at least, a new IND. This represents a new drug product or a new biologic and I would have it go through a full extension IND-enabling program.

It does not represent, to me, any type of generic biologic or follow-on protein therapeutic.

DR. CAVAGNARO: But I would argue it represents a potentially real innovator situation.

DR. O'NEILL: What it represents--well, the follow-on--

DR. CAVAGNARO: Whether a scale-up change, manufacturing or something.

So take it into consideration now as an innovator. What would you do?

DR. O'NEILL: I would look at it in this manner. The biochemical characterization of this product is not--represents to me that the process is not well understood or well in control in that

the characterization cannot be comparable to the innovator molecule.

DR. CAVAGNARO: Is that what you would argue to the FDA in a phase three trial? If this was scale-up and this is your product, is that the argument that you would make to the FDA, that the product was very different, that you shared biological activity and it was PK and now you've just scaled up in manufacture for your phase three material and you see this little change here?

DR. O'NEILL: I'm assuming that the biochemical characterization is not within the specs of the innovator company.

DR. CAVAGNARO: I'm just drawing--I heard your point in terms of innovator versus follow-on. Now, I'm asking the question, if you, as an innovator company, going across your product, scale-up, change in manufacture, change in cell line, whatever might happen within your program, as an innovator company.

Do it as an innovator company. Forget about the follow-on.

DR. O'NEILL: And there was a different in the biological characterization due to some process change, some cell line change, whatever.

DR. CAVAGNARO: We're not talking--that's a soft kind of--it's enough that it gets thrown over to the pharmacology and toxicology department to do something with.

DR. O'NEILL: I would go off the characterization, off the history of the data, on the innovator molecule and if my process change or my cell line change led to a biochemical characterization that was not equivalent, I would send it back to the process sciences to try and find a way to get this characterization to match up in one way, shape or form or another.

It represents a horrible risk to take that type of molecule forward into the clinic, especially in a post-marketing or commercial situation.

DR. CAVAGNARO: You're very brave in terms of your phase three program.

DR. CHAMBERLAIN: Just a follow-up. Jim

Green knows better than anybody in this room, maybe Avonex would fall into that bag, physicochemical differences between the first and the third versions.

Small differences may be in PK/PD, but an acceptable clinical safety/efficacy profile over the long course of time.

DR. GREEN: I was waiting for somebody to bring that one up. That's actually a pretty good example and it gets to actually something that I would talk about as the term well characterized.

People come at this definition of well characterized from their own didactic training. Folks that tend to be analytical gurus and biochemical folks believe things can be well characterized, and I think that was the operating theme a decade or so ago.

The fact of the matter is this kind of scenario, which is indicated here, reflects all too often that these kinds of changes we really don't understand.

Now, are you willing, as an innovator,

essentially, to take the stance that you can override differences that are on a biochemical scale with other data sets, as indicated here, biological activity, kinetic disposition profile.

Myself, personally, I would feel comfortable in that sense that perhaps qualifying, if the dosimetry lined up, if the kinetics lined up, if the toxicologic profile lined up, if the initial clinical assessment lined up, that we probably don't know essentially enough what those changes mean which are being detected on a biochemical level.

To be quite honest, those kinds of changes, more often than not, we don't understand what they mean. We don't have the product attributes defined as explicitly as we like to talk about, that we understand these from a pure structure-activity perspective. We just don't.

That's why once a product essentially is marketed, one of the first questions that the agency always gives us is give us your next 30 batches worth of history and we'll come back and

refine the specifications, because that's only based on experience.

So I think it gets to how different is different based upon that assessment initially.

Right out of the box, because a follow-on company starting with a new cell line, new process parameters, the fact that you saw these kinds of differences, I wouldn't be surprised.

It really depends on what they mean in the broader context of the other assessments. You'd like to have not those differences to deal with because you could be surprised later on, but I think it depends on what you can bring to bear to interpret what they mean.

DR. WEIR: I think it depends, in part, on the nature of the differences and if the other data can back up what the actual biochemical differences means, including the non-clinical PK data, as well as the tox data, and even though there might be a concern, I think that could be addressed, in part, possibly, through doing a more conservative clinical trial as opposed to taking the follow-on

product and pushing it back to being a whole new IND.

Of course, all of these have to be considered on a case-by-case basis, what the nature of the differences are, as well as how much supporting data there are, and then I think evaluate what are a number of approaches that are reasonable.

DR. GREEN: Interestingly, Dr. Kozlowski's comments this morning, I think he said that right off the bat, and that slide that he showed, if you failed, essentially, on the identity test, immediately, he said, it's a new product. So that's a little bit even different interpretation than the one I addressed.

DR. WEIR: How different does it have to be before it fails? Is it just one small difference? From the pharm/tox perspective, I rely a lot on the CMC reviewers to better define exactly what--is that change considered to be a meaningful change as far as it being a different product chemically and biochemically.

DR. CAVAGNARO: Right. Is it different and does it make a difference?

DR. WEIR: In this scenario, does anybody

feel that a different approach would be warranted or a more stringent approach would be warranted for a high versus narrow therapeutic index?

It seems that there is already concern. If it was a product that had a narrow therapeutic index, that would push toward even more concern. I don't think there's anybody that holds a different opinion. I wouldn't think so.

And about complexity of molecule, I think, certainly, if the molecule is less well understood and there is less historical experience with just targeting a particular system in general, that certainly would heighten concern.

Any other comments or points to address with this?

DR. HORA: Maninder Hora, from Chiron. I just wanted to point out, on your comment about how different is different. I think as an innovator, when we are doing our preclinical and clinical

development support, process scale-up and so forth, sometimes we come across some variants, some species, and we are asked to do specific studies to address those, and they are infrequent, but they do happen.

I'm wondering that a follow-on protein manufacturer comes here and then they see, for example, let's just take aggregation. Aggregation can be arrived at scores of different ways. You can have non-covalent aggregation going into covalent aggregation, then going and becoming particles and so forth.

Now, there is a limit on aggregation in the product, but when a follow-on company comes in, they are not aware of how the original innovator has been approved, on what basis.

In those circumstances, the FDA knows a lot more about such issues and I'm wondering how those issues would be tackled onto.

For example, in this case, I would say depending upon how different is different, those kinds of studies would be necessary.

So the issue is how would that be pursued.

DR. WEIR: Aggregates, specifically, one of the concerns that comes to mind with aggregates

is, of course, immunogenicity. I think there has been some discussion of how meaningful and reliable the immunogenicity studies for comparative purposes are in animals. That would be one approach to take for addressing aggregates.

I'm not really familiar with aggregates offhand. One of the other panel members, Jim or Joy.

DR. HORA: Biodistribution could be different and that could relate to potency, as well.

DR. CAVAGNARO: I guess I'm not exactly sure of the question. So if, as was suggested this morning, that what you really need to do is look at a number of batches and try to understand physiochemical, biochemical characterization.

So if you were to do that and say you had a number of batches of the innovator and you would look at their aggregation, percent aggregation, and

then the follow-on would derive some range of acceptable aggregation, but, of course, you wouldn't know anything about stability and whether or not aggregates increase or whatever.

So the question is doing animal studies to assess aggregation; is that the question?

DR. HORA: Well, I think it also relates back to the inability to completely define the nature of aggregate, for example, if you're talking about aggregates, because as I was pointing out in the physicochemical discussion, that an aggregate is a distribution.

You can get a number by different ways, by a composite of small, large, medium aggregates. You can get a number and that number could be matched or fortuitously is matched.

But the differences could be shown by preclinical methods under certain accentuated conditions.

So if the experience is limited here, and so you haven't seen those conditions which define the boundaries of such behavior, and I think that

is where I get stuck here, because how would you predict those situations and how would you advise the follow-on company to address those issues.

DR. GREEN: For example, and maybe this might help get at this, a follow-on company, again, within the context of a head-to-head comparison, would have essentially the product of whoever they're going to compare.

That could be characterized with some degree about what the aggregate profile is and characterize it as best they can.

The first thing, recognizing that all aggregates aren't the same, and they change essentially with conditions of storage.

Seeing that, first and foremost, the concern that people associate with that is the immunogenicity issue.

Now, do aggregate profiles within the test--at least the paradigm testings that we're talking about, nonclinical toxicologic assessments, can they provide relevant information?

Well, if the innovator product--again, it

gets back to the example that I cited earlier. If it happens to be a product that does not have an immunogenicity profile or a low immunogenicity profile and its aggregate profile is this, is characterized as this profile, the follow-on company, essentially, testing in a head-to-head comparison, what is that immunogenicity profile.

If it is recognized or proven to be much higher in the context of that test system, you may conclude that it's related to a different aggregate profile, antigen presentation, all of those kinds of issues that might be going on.

That is a signal and that signal should be interpreted within the context of the overall assessment.

Now, if I were sitting at the FDA, I would look at that signal and I would say I'm not sure what the relevance of it is. However, I might want to look more closely and more carefully and more robustly at immunogenicity issues for that product than perhaps another product that didn't have that kind of profile.

I think that's the extent of what you can prove.

DR. HORA: Thank you.

DR. CHAMBERLAIN: I think the panel are asking the right questions and I think, yes, logically and scientifically, if the therapeutic index is rather narrower, then you do have to design your head-to-head comparisons with more groups, simply, more doses of the reference versus the test.

But I'm struggling to think of concrete examples of biologics on the market for which you would do that. So I think there is a difference between the theoretical and the practical when it comes to the class of biologics that we are talking about. So I would be interested in hearing the panel's view on that.

Are there particular biologics where you could see a case for, based on therapeutic index considerations, you would design your head-to-head comparisons more robustly in the quantitative sense?

DR. CAVAGNARO: I don't know what's off the table in terms of you said that, but I think that one where we are particularly concerned with our fusion toxins or monoclonal antibody toxin, where we know that the shape of the dose response curve is very--now, I don't know if you can--that's

a highly complex molecule. I don't know if anybody would ever want to make a generic.

So that's kind of the idea that we are thinking about.

DR. CHAMBERLAIN: I'm thinking of those outside the realm of this discussion, really. I tend to think of any antibody related products as being outside of this particular discussion, rightly or wrongly, and, secondly, immunoconjugates, there are a number of ways of deriving those, which make them new molecular entities in their own right.

So I was trying to focus on the growth factors which are already marketed. Even for activated protein C, that might fall into the category, but I'm not sure if I would design my

studies any differently from a G study or on EPO.

DR. CAVAGNARO: So I guess the question is whether or not toxicity studies are useful in terms of--

DR. CHAMBERLAIN: The question that you asked was does therapeutic index actually make an impact on the way you design those comparative tox studies.

DR. GREEN: I think the way I think about therapeutic index is particularly for a product that has a narrow therapeutic index, on the prior assessments, which might be concluded as being small differences, that would make me more concerned and I would start asking questions related to what do I know about those differences.

For example, even if you saw changes--and we know the biochemical characterizations. There's always skewed data. I mean, there's just always skewed data.

The biological activity, perhaps a little bit more potent. Then perhaps you're getting an indication that some batches have been a little bit

more potent.

And if the kinetic comparison did not line up, did not match fairly strict criteria for a narrow therapeutic index drug, in aggregate, I would be more concerned in that situation, dealing with a narrow therapeutic than one that has wide, just because of the degree of uncertainty.

DR. CAVAGNARO: And I think it was more for the wide therapeutic index whether or not the tox study would be meaningful in terms of value added to detect a difference.

So if we have proteins that are, quote-unquote, nontoxic and then the value added of doing a toxicology study as a sensitive assay to distinguish, I think, more so in that end.

DR. WEIR: Any additional comments on case two? Joy will come in with case three.

DR. CAVAGNARO: Case three is a variation of case one, actually, where we have the same similar biochemical characterization and similar biologic activity, and now, unlike case one, the PK is different.

Now, an argument has been put forth that in terms of clinical pharmacology, that, well, we're going to go into humans anyway and if we're

going into non-human primates as our model species, the end is not going to be sufficient to actually be able to address similarity.

You may have a better chance with rodents if you can--with more animal numbers. So there is a liability here of perhaps seeing a difference and really the difference not being meaningful.

So what's the added value of doing an animal study if you may get something different? Just go ahead and go right into the clinic and ask the question.

DR. CHAMBERLAIN: I think you have asked another very helpful question, and I think the lead on from that is the way I would interpret that scenario, is to actually look at PK in more than one species in the nonclinical setting, because I really want to understand whether it's a species restricted or not.

I think if we see a difference between the

innovator and the follow-on product in a preclinical setting, we need to understand the basis for that before we go on.

DR. ROGGE: Mark Rogge, ZymoGenetics. I guess, in my experience, the clearance mechanisms, if we want to just focus on clearance, for example, when we're talking PK here, they are generally well conserved and if you see a change in one direction, for example, in an animal species, it's relevant, it's probably going to change that direction in humans.

Now, it may not change by the same magnitude, but it's probably going to change in that direction, and, again, thinking about when those changes occur in serum is probably indicating that changes are occurring somewhere else, in tissues or organs where there may or may not be safety or efficacy occurring.

So I would, personally, in this situation, go forward with some kind of tox evaluation and try to understand why those differences might be occurring.

DR. GREEN: Can I add a comment to that? I think this example essentially is particularly telling and, I would say, concerning, because the

premise here is that the information that has gone before on an innovator, an innovator has to be picked, basically, that all that information can be leveraged, in the case of the follow-on product, in order to streamline the development program.

If this kind of profile proves that, on an analytical laboratory basis, we don't understand the level of product attributes sufficiently to predict a change in dosimetry, as reflected by kinetics, you have a different product; therefore, you have different dosimetry. It would be highly unlikely that you would be able to match the innovator label, I would think, with respect to dose and regimen and all those other considerations.

So this is the kind of information that the earlier you know it, you know what you're dealing with, and, essentially, we would be able to then gauge the scope of your program with respect

to all the considerations for therapeutic index, et cetera, as well as the clinical dosimetry.

So this would be a profile, I think, of concern.

DR. CAVAGNARO: And I guess that would be based on whether or not the study was--again, I think the concern is if you're going into non-human primates, people have done statistics in terms of how many animals that you need.

Theresa, you probably have the number. It's a huge number of non-human primates, and that is an important thing to understand. This may be different because somebody has just done a study and it's different, it's not really different, it's that somebody didn't want to use 60 monkeys to look at.

So that is why it's really important, when you design studies, if you're going to use the data, that it's real.

This relates to a real difference or a difference because of the study design that is perhaps not robust enough.

DR. GREEN: And I think what is important here is the amount of--and I think a follow-on company, as well as an innovator, I mean, they

don't only do one study. There is a data set that essentially is generated over time. It is within the context of this change against what you understand about the product.

I think what we're talking about are, essentially, significant, what would be viewed as physiologically significant differences in disposition that make you think about the concept of dose differently.

Once you've crossed that line that the dose is different, I think you're on very shaky ground, leveraging all that dosimetry data that's been generated in different settings.

DR. CAVAGNARO: Is Mark Rogge still here? We're talking just about PK differences. Do you feel that there are any in terms of--do we have to look at more than PK distribution?

DR. ROGGE: I would agree with what Jim said. Clearly, if the PK is different, they're

different products.

Following up on my last comment, as either, say, an innovator or the person trying to create this follow-on protein, I would be trying to understand why there is a difference.

I wouldn't necessarily personally feel comfortable moving it forward through a full tox program and human program, whatever that might be, because, fundamentally, it's not a follow-on to the innovator's product.

But I would want to understand why is there that difference.

And I think there's something else that hasn't been brought up, and it's the wholesale proteins that are carried along with all these products.

One thing that we are finding is that that can have an impact on the immunogenicity of these molecules, as well.

So I would like to throw that into the fray, if there is time either now or later on to talk about that.

DR. CAVAGNARO: Right. Well, that relates to some of the adventitious agent issues, as well. I mean, basically, you should clean it up.

You know what I mean. You're right.

DR. ROGGE: Oftentimes with a change in the process, you're not necessarily getting more wholesale proteins, but you're getting different wholesale proteins, which is where I'm coming from.

DR. CAVAGNARO: Right.

DR. HORA: One line of thought would be is biochemical characterization in this case sufficient. Have you explored all the possibilities to look at the molecule in all different ways?

One of the thoughts that I would have is can we apply more techniques, different assays and see some differences.

DR. CAVAGNARO: So if your pharm/tox group came up with a difference in PK, they would throw it back to you and then you would try to--

DR. HORA: Right. As an innovator, that is what we end up doing. We try to find

differences which may not have been seen in the first set of assays.

DR. CLAUSS: Clauss, from Baxter. It is more a general question about head-to-head toxicological or animal study to be conducted. The innovator's product is not available and pure. It is available as the formulation which is provided for patients.

Therefore, it is going to be very difficult to run a head-to-head comparison. For example, you're talking about PK. How are you going to make the comparison? In fact, you're going to compare a formulation, not a product, a pure product, against another product which may be pure, in this case.

So, in fact, for tox, in general, you're going to test the formulation. So HSA immunogenicity, as an example, how are you going to be dealing with that element here for PK? If you have a change in your formulation, you will have an impact on your PK, so it will not be a surprise.

So I just wonder how is it possible to get

these studies to be conducted very practically.

The second point is as you have been saying before, many of the proteins which are human recombinant proteins have a very low toxicity in animals. They are sometimes high immunogenicity, but very low toxicity on animals outside of their activity.

Is it really making sense to go for a high level of animal studies in this case? Is it going to provide additional information or additional safety at that level?

So I just don't know, but I'm really asking the question.

DR. CAVAGNARO: So, Mark, you're a card-carrying kineticist. I mean, I think that is a challenge. I think in terms of--so the first question is the comparator. Within even an innovator program, the idea of comparison, and those of us, past agency folks, in terms of this concept of biocreeping, what's the same, the first, and then you compare it to the second, and now you compare it to third and is the third the same as

the first, but you better have residual material so you can do the bridging studies.

But now you come along and you're doing this comparison now with the formulation. How can we deal with that?

So we've leveraged the information as we go for the formulation. I mean, that's the whole concept of it. You leverage the data if you have something to compare with, but if you don't have anything to compare with.

DR. ROGGE: It's a good point. The innovator companies do have the luxury of sometimes some very large databases.

As I said in my talk this morning, even if it's fundamentally not required, from a regulator's standpoint, to do some PK work or immunogenicity work, whatever, we'll do it, irrespective.

But it brings up other issues, as well, because as these components change, you are finding yourself also needing to generate new antibodies for the assays and try to create standards sometimes when standards don't exist.

So it is a challenge, it's a big challenge, but at the same time, we've found that it adds a lot of value.

DR. CAVAGNARO: So the point about the formulation piece of it, can one ever compare innovator, a follow-on to an innovator if there's a different formulation?

DR. ROGGE: Well, I don't know what a lawyer would say to that in terms of the follow-on protein product, whether the formulation is part of that or not.

I gave that example this morning and, yes, obviously, you can do the study and you can show there are differences, but I think at least for several more years, you will find it difficult to use that formulation for Avonex, because it's under patent, with my name on it.

DR. GREEN: I might add a couple points. I think this, again, gets back to the fact that these are hierarchical assessments and whether you can do something or not depends on what the data shows you--what has gone before.

I would say for a simple kinetic comparison, with the existing formulation and your formulation, that study can be run at pharmacologically relevant doses.

Let's say you saw essentially a difference in bioavailability from the innovator's product of

50 percent to 80 percent, essentially, with the follow-on product, and you are concluding it is formulation-dependent.

Well, that may prove that those formulations essentially are behaving different, dose preparations are behaving different on the basis, essentially, of solely formulation. You have an answer to that question.

Now, can you progress that essentially into toxicologic assessment? Depending on how you equate the dose, you could correct for that difference in bioavailability, if that's the route you wanted to use, you could do that study.

What you are limited in sometimes is the multiples that you could use, because of the formulations that you can purchase. However, a

pharmacologically active formulation, 1X, 5X, something like that, certainly conceivable, certainly doable, and, in fact, you could conceive of doctoring the formulation if there were ingredients that you knew that were in that formulation that you could add to it.

So all of these steps can, in fact, be taken.

Now, the other point about the large therapeutic index, I think I'd like to just make one comment.

I think for many of the products that have been approved within the recent decade, I think the assessments that have been done, from a toxicologic perspective, have generally probably been very thorough. We've got experience with the S6. We've got more experience with different regulatory authorities assessing these products, and the standards, in fact, have been raised.

Your comment about most of these things being safe, some of the old products were not sufficiently tested. Some of the pleiotropic

effects of many of the interferons were never identified in animals because those animals were never studied at pharmacologically active doses until product, in fact, was available, and, lo and behold, when those studies were then repeated, the hepatotoxicity was seen, the bone marrow suppression was seen.

What do you see in the clinic with high dose interferon exposure? Those same human toxicities.

So I would be careful, essentially, about the safe, the large therapeutic extrapolation. I think we have learned a lot about some of these other molecules, and they all certainly aren't safe.

The myth that I like to think, if it's natural, it must be safe, certainly is not true, because there are plenty of examples that prove that otherwise.

DR. WEIR: I'd like to add one comment regarding the formulation. I think that using the clinical formulation is the appropriate step to

take. I mean, ICHS-6 clearly states the formulation should be as close as possible.

If you're talking about an innovator, there might be, as clinical development progresses, there certainly can be changes made in formulation, but starting out, you really need to be ideally identical to.

There can be some minor differences, but I think if you're looking at being a follow-on product and you do a PK comparison, you use your formulation and compare that to the clinical formulation that is available, and there's differences, maybe those differences are due to formulation and you can go back and, as Jim was saying, doctor formulations and try and figure out what it is.

But I think you really do, if you're doing a head-to-head comparison, you really need to use the formulation that is the current innovator formulation in order to do the appropriate scientific comparison.

DR. EL-HAGE: We, as a group, came up with

a few summary slides, but I'd like to comment, there was some comment from the group after I presented them last time, that this in no way represents the agency's interpretation of what may be needed.

This was kind of the consensus opinion of this panel and our multiple discussions of the topic.

Basically, we had two summary slides and they summarized product attributes that would be supportive of a minimal, nonclinical safety evaluation and product attributes that would warrant nonclinical safety evaluations on a case-by-case basis.

So some of the attributes that we thought might generate the need for a minimal data set would be that the biochemical characterization confirms identity; that the molecule is a low complexity protein; that there is comparable PK, either nonclinical or clinical or both; well understood mechanism of action; extensive pharmaceutical knowledge and experience; and, that

the protein was a replacement therapy or had a large therapeutic index.

A case example of something that we felt would fall into this category would be the protein products that are in my division, the insulin products, growth hormone products.

There's multiple approved products, with large clinical safety databases, multiple manufacturers, multiple host cell lines of production, and, in our experience, there haven't been any, even though there are product differences for this class, there haven't been any clinical safety consequences, and most of these products had various levels of preclinical workups, anywhere from three-month monkey studies to the full tox battery, but there were no significant safety issues in those studies, as well; and, what would we consider perhaps a minimal tox workup.

I think what we considered as a study that might incorporate multiple end points, a two to four-week study, looking at PK, PD, standard toxicology safety assessments, local tolerance,

and, ideally, maybe some comparative immunogenicity.

Then product attributes that would warrant more extensive nonclinical safety evaluations, and I think we discussed a lot of those today. Those would be high molecular complexity or a lesser ability to characterize those proteins by standard biochemical methodology; new process impurities; moderate to high heterogeneity; PK differences; changes in formulation; changes in route of administration; mechanism of action poorly understood; limited pharmaceutical experience, that is, a single approved product with limited clinical experience, or a narrow therapeutic index.

I don't remember if I made the comment, but they have reopened the docket from the fall follow- ons meeting, and they ask that if you have any specific comments related to this issue, you can submit them formally to that docket for consideration and we will include those in the comments from the meeting.

Thank you for your attention, and

particularly for those who sat through both sessions, you are congratulated.

[Whereupon, at 4:56 p.m., the meeting was concluded.]

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